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Central apnea in a sporadic case of Creutzfeldt-Jakob disease with brainstem involvement

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Abstract

We report a patient with Creutzfeldt-Jakob disease with somnolence as an initial manifestation and sleep apneas as a prominent sign. A respiratory polygraphy revealed the presence of a continuous Cheyne-Stokes pattern both awake and during sleep with central apneas. The neuropathology showed PrP deposition in brainstem involving respiratory nuclei. Central apnea is a rare manifestation of CJD that can be observed from early stages and may be related with PrP deposition in brainstem structures.

Key words: Creutzfeldt-Jakob; central apnea; respiratory polygraphy; neuropathology; brainstem.

Introduction

Creutzfeldt-Jakob disease (CJD) is typically characterised by dementia, myoclonus, ataxia, visual disturbances and motor dysfunction with a rapidly progressive course. Neuropathology reveals diffuse spongiosis, neuronal loss, gliosis and a variable degree of protease-resistant prionic protein (PrP^{res}) deposition in several locations including the brainstem. The most usual clinical presentations are dementia, ataxia and visual symptoms (Johnson, 2005). We report a sporadic case with prominent hypersomnia and central apneas, documented with respiratory polygraphy and neuropathological study.

Case history

A 58-year-old Spanish man presented with gait instability and falls, dysarthria, hypersomnia, observed sleep apneas and night confusion, which started four months before. He had a history of mild chronic obstructive pulmonary disease and chronic alcoholic hepatopathy and was receiving citalopram and sulpiride. The initial examination only revealed ataxia and dysarthria. Routine examinations were normal, and cranial MRI only showed cerebellar atrophy. A domiciliary nocturnal oxymetry showed an oxyhaemoglobin desaturation index of 74/h and CT-90 compatible with obstructive sleep apnea syndrome. The neurological signs were initially attributed to alcohol and psychotropic drugs, but three months later he was admitted to the Department of Pneumology because of intense progressive somnolence. Arterial blood gases revealed deterioration (pH 7.37, pO2 64 mmHg, pCO2 51 mmHg) and a Cheyne-Stokes breathing pattern was observed. A respiratory polygraphy was performed during daytime sleep (siesta), revealing the presence of a continuous Cheyne-Stokes pattern during sleep and also when the patient was awake during examination, with periodic breathing and central apneas and, to a minor degree, hypopneas (Fig. 1). Only a minority of the events showed a concomitant obstructive component (added snoring). The apnea-hypopnea/hour index was 102.

The patient had also experienced a worsening of ataxia and developed urine incontinence and cognitive impairment, and was referred to the Department of Neurology one month later. Neurological examination showed bradypsychia, disorientation, vertical upper gaze palsy, bilateral dysmetria and dysdiadochokynesia, pathological Stewart-Holmes manoeuver, generalised hyporeflexia, dysarthria, severe ataxic gait, myoclonus that exacerbated with acoustic stimuli and digital myoclonus. EMG revealed a severe axonal sensory-motor polyneuropathy, probably of alcoholic origin. Routine examinations were normal but 14-3-3 protein was found in CSF. EEG showed signs of diffuse neuronal

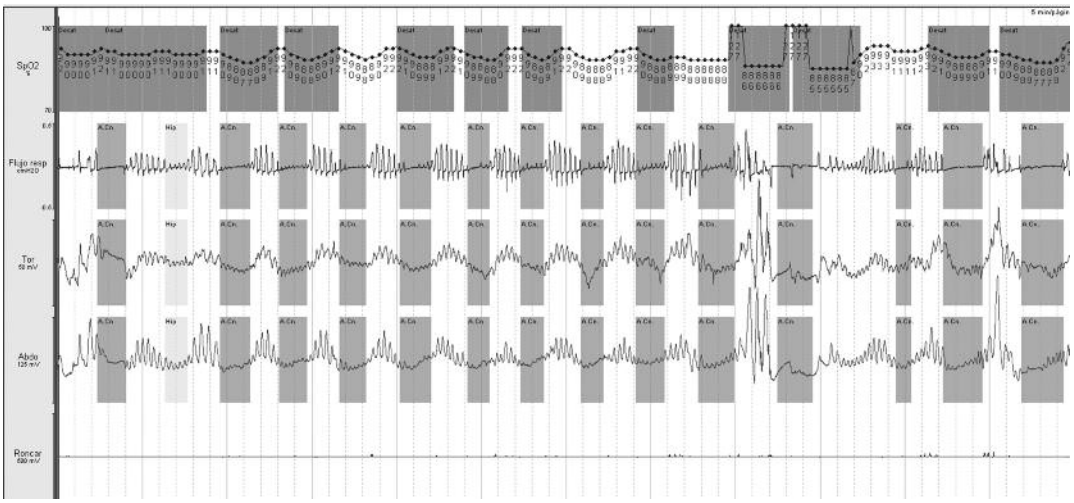

FIG. 1. — An example of the Cheyne-Stokes pattern seen in the patient. Note the crescendo-decrescendo pattern on nasal flow, and on thoracic and abdominal movements, with central apneas in the decrescendo phase. SpO2: oxyhaemoglobin saturation; Flujo resp: nasal flow; Tor: thoracic movements; Abdo: Abdominal movements; Roncar: snoring.

dysfunction but not periodic complexes. Cranial MRI showed hyperintense T2 signal alterations in caudate, putamen and cortex and cerebellar atrophy. A diagnosis of CJD was made. No mutations were detected in the 51-91 region of the PrP gene, and the patient was heterozygous for the Met/Val 129 polymorphism. The patient progressively worsened and died 2 months later. The neuropathological study showed neuron loss, confluent spongiosis, microgliosis and astrocytic gliosis in the cerebral cortex, striatum, thalamus, amygdala, basal nucleus of Meynert and cerebellar cortex. Synaptic-like PrP^{res} deposition was found in all these regions, as well as in the substantia nigra, locus coeruleus and pontine nuclei. Relevant to the present clinical findings was discrete neuron loss, microgliosis and PrP^{res} deposition in several nuclei of the medulla oblongata including the caudal and rostral ventral respiratory group, and the dorsal respiratory group (Fig. 2). Western blots of cerebral cortex homogenates showed a type II band pattern of PrP^{res}.

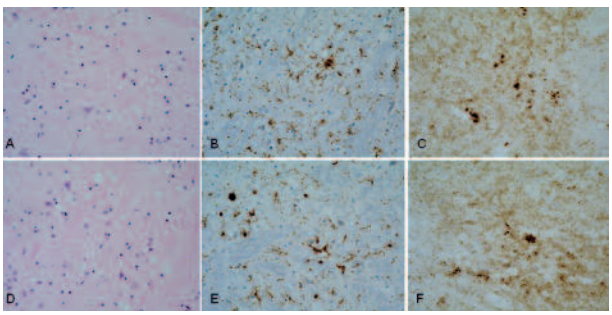

FIG. 2. A-C. — Rostral ventral respiratory group; D-F: caudal ventral respiratory group. A, D: haematoxylin and eosin; B, E: CD68 for microglia; C, F: PrP^{res} immunohistochemistry. $\times$ 400.

Discussion

A similar case was reported by Iwasaki (Iwasaki *et al*., 2006), who described a patient that presented with dysarthria, dysphagia, lethargy and sleep apnea and developed hypercapnic respiratory failure with a Cheyne-Stokes pattern (documented only by physical examination). The brainstem was preserved from spongiform degeneration and gliosis but affected with PrP deposition and microglial activation, and the authors speculate that such changes even without obvious neuronal loss were responsible in part for the clinical signs. Another case of sleep apnea has also been reported by Mamdani (Mamdani *et al*., 1983) in a CJD patient who developed sleep apnea in late stages. Neuronal degeneration and diffuse astrocytosis were seen in the nuclei pontis and reticular formation suggesting that the apnea could not be incidental. We report for the first time central apneas, not only during sleep but also in wakefulness, documenting central apneas with respiratory polygraphy and involvement of respiratory nuclei with neuropathological study.

Accumulation of PrP in the brainstem is an early pathological event in sporadic CJD (Iwasaki *et al.*, 2005). CJD typically presents with dementia, ataxia or visual disturbances (Johnson, 2005), and central apnea is a rare manifestation that can be observed from early stages and may be related to PrP deposition in brainstem structures.

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